VIBRATIONAL SPECTROSCOPIC, DFT CALCULATIONS AND MOLECULAR DOCKING STUDIES ON POTENTIAL BIOACTIVE AGENTS

A SYNOPSIS

Submitted by

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(Reg. No. 201715235)

in partial fulfillment for the award of the degree of

DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSICS

SCHOOL OF ADVANCED SCIENCES

KALASALINGAM ACADEMY OF RESEARCH AND EDUCATION

(DEEMED TO BE UNIVERSITY)

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TAMIL NADU, INDIA

JUNE 2022

1. INTRODUCTION

Over the past several years a great deal of work has been carried out on different organic compounds of biological and pharmacological applications. Molecular spectroscopy explains various methods for the better understanding of molecular motions of polyatomic molecules. Modern spectroscopic methods become a powerful tool in the investigations of the physical, chemical, thermodynamic properties and nature of interatomic forces in the molecules [1]. The vibrational spectroscopy is also useful in the identification of functional groups and the strength of the chemical bonding between atoms. The philosophy of computational methods of vibrational spectroscopy significantly changed after the introduction of quantum chemical calculations [2]. This has opened the way for calculating the frequencies and intensities of spectral bands. The vibrational and rotational energies of the molecules can be studied by infrared and Raman spectroscopy. The infrared and Raman spectroscopic methods mostly yield complementary types of information. For a complete vibrational analysis, both methods should necessarily be used. When an infrared light passes through a sample, some of the frequencies are absorbed while other frequencies are transmitted through the sample without being absorbed. The percentage of absorption or transmission against frequencies is the resultant IR spectrum. In order to obtain Raman spectrum now-a-days, powerful laser sources are used for excitation of the sample. The absorbed frequencies obtained from IR and Raman spectra along with structural parameters are used to carry out the normal coordinate and conformal analysis of cyclic and heterocyclic molecules [3].

Density functional theory (DFT) calculation has emerged in the past few years as successful alternative to traditional Hartree-Fock method. The DFT methods, particularly hybrid functional methods [4] have evolved a powerful quantum chemical tool for the determination of the electronic structure of molecules. In the frame work of DFT approach, different exchange and correlation functionals are routinely used. Among these, the Becke-3-Lee-Yang-Parr (B3LYP) combination [5,6] is the most used since it proved its ability in reproducing various molecular properties, including vibrational spectra. The combined use of B3LYP functional and standard various basis sets, provide an excellent compromise between accuracy and computational efficiency of vibrational spectra for large and medium size molecules. In this work, the vibrational spectra, DFT calculations and molecular docking studies are carried out for potential bioactive agents.

2. LITERATURE REVIEW

The reviews of literature for the selected biomolecules in this study are detailed as follows:

2.1. 2,3-dichloro-1,4-naphthoquinone

The biological activities of compounds containing quinone groups find active agents against many diseases and the electron donor acceptor phenomena of quinones were studied due to their potential non-linear optical activity. By the introduction of chloro, cyano groups with naphthoquinones, the electron affinity properties were enhanced [7,8]. Recently, the antifungal and anti-bacterial activity of the nucleophilic substitution reactions of 1,4-naphthoquinone derivatives have been studied [9]. Moreover, the biological evaluation, antioxidant and cytotoxic activity of substituted 1,4-naphtho and benzoquinones have been investigated [10]. Further, the electron attracting and donor accepting property of the quinone affected the redox properties and modulated it which is responsible for the oxidative stress [11]. More recently, the electrophilicity of the naphthaquinone can be increased by the substitution reactions due to the intramolecular bond formation between the terminal groups [12]. In the same way, the compound 2,3-dichloro-1,4-napthoquinone (DCNQ) has many special properties and some unique characters because of the structure of quinone, which are naturally found in many derivatives. Hence, in the present investigation, molecular geometry, optimized parameters and vibrational frequencies of DCNQ are computed and the performance of the computational method for B3LYP with the standard 6-31+G(d,p) and 6-311++G(d,p) basis sets are compared.

2.2. α-santonin

α-santonin contains many isoprenes and shows numerous biological activities such as antipyretic, anti-inflammatory, anthelmintic, and anti-fungal. The functionalized ring with lactone and dienone systems leads the molecule in important anticancer activities [13]. Also, α-santonin allows many centres for reactivity that offer chance for more chemical alterations to generate novel drug systems [14]. As of now, the spectroscopic examination and DFT calculations of α-santonin were detailed [15] but no molecular docking investigation and further studies have been carried out. Thus, an endeavor has been made to investigate the role of α-santonin for improving the treatment of SARS-CoV-2 and cervical cancer by molecular docking. The other molecular properties of α-santonin have been performed by the DFT-B3LYP strategy, which can support pharmaceuticals and natural drugs.

2.3. 4-hydroxy-3-methylbenzoic acid

Benzoic acid derivatives have been attracted towards many biomedical properties such as antiviral, antioxidant, antitumor, antifungal, antimicrobial, anti-inflammatory, radical regulating, hepatoprotective and cytoprotective effects [16-18]. They are also used in identifying the fibrotic skin disorder, gastrointestinal disorder and in the medication of drug against ultraviolet radiation [19]. Recently, the motivating features of benzoic acid derivatives have pulled many researchers to take up research in the field of spectroscopy [20-22]. More recently, the spectroscopic properties of metronidazole metal complexes with benzoic acid derivatives have been investigated by Tella *et al*. [23]. However, the literature survey reveals that the spectroscopic investigations of 4-hydroxy-3-methylbenzoic acid (HMBA) along with the DFT calculation have not been reported. Hence, in the present investigation, DFT based quantum chemical calculations for optimized geometrical parameters and wavenumbers are calculated and the performance of B3LYP/6-311++G(d,p) computational method are matched with the experimental results.

2.4. 3-methoxy-2,4,5-trifluorobenzoic acid

Benzoic acid is the standard chemical used in bomb calorimeter to determine the heat capacity. Benzoic acid enhances the growth of mold, yeast, bacteria. Skin diseases are treated by benzoic acid [24]. Topical antiseptics and inhalant decongestants products are mainly based on benzoic acid derivatives. Further, in food preservatives [25] salts of benzoic acids utilized. Benzoic acid derivatives are also used to diagnosis gastrointestinal complaints and fibrotic skin disorders [26] to protect from UV radiation. The chemical and pharmaceutical industries prepare substituted benzoic acids by the oxidation of corresponding substituted toluene [27]. From the patent report, it reveals that benzoic acids selectively control the tumor tissue [28]. The interesting features in spectroscopic area of benzoic acids and their derivatives have been already studied by many researchers [29,30]. Hence, owing to the important and significant features of substituted benzoic acids, a detailed study on spectroscopic research of 3-methoxy-2,4,5-trifluorobenzoic acid (MFBA) was carried out.

2.5. 2,4-dimethoxyacetophenone

Acetophenone is one of the aromatic carbonyl compounds which are having interesting photochemical properties [31]. Like organic NLO materials acetophenone plays an important role in frequency mixing, electro-optic modulation, optical

parametric oscillation and optical bi-stability [32]. A study on the 20 acetophenones with their structural characteristics by using electronic and topological indices revealed their antibacterial activity [33]. Also, the substituted acetophenones acts as a synthesis reagents of several organic reactions [34]. Because of the versatile applications of acetophenones, the numerous experimental and theoretical studies have been made on the vibrational spectra of acetophenone derivatives [35-37]. Recently, the investigations of acetophenones from acetophenone hydrazones using ultraviolet radiation and chlorinated solvents have been studied by Martins *et al.* [38]. Consideration of these factors, an attention has been turned towards 2,4-dimethoxyacetophenone (DMAP). To the best of knowledge, no DFT frequency calculations for DMAP have been reported until now for the frequency assignments. Therefore, in this study, the vibrational spectra of DMAP along with DFT calculations have been performed to identify its various normal modes.

2.6. 4-nitroimidazole

Nitroimidazoles are key molecules with extensive range of activity and therapeutic potential. A plethora of nitroimidazole based drugs are available for the treatment of bacterial and protozoal borne infections [39]. They belong to a group of nitroheterocyclic compounds that have broad spectrum activity against a series of organisms such as mycobacteria, anaerobic Gram-positive and Gram-negative bacteria, and some of them have already been used in clinics or under clinical trials for the treatment of infectious diseases [40]. Further, the derivatives of imidazole act as energetic materials for civil and military applications when they have more than two nitro groups [41], specifically 4-nitroimidazole. Due to its significant features in recent times, numerous experimental and theoretical studies have been made on the vibrational spectra of imidazole derivatives [42-44]. The vibrational spectra reveal the exact biological process and the complex process which takes place in the imidazole derivatives. In the present investigation, the complete B3LYP comparative report on the vibrational spectra of 4-nitroimidazole (NIM) was performed to derive information about its electronic effects and intramolecular charge transfer.

2.7. 5-nitrobenzimidazole

Benzimidazole subordinates have lofty catalytic movement and utilized as catalysts in dissimilar coupling responses [45]. They are considered as a heterocyclic organic compound in which the benzene ring moiety fused by 4,5 position of imidazole framework. They are extremely beneficial intermediates within the

evolution of pharmaceutical activities for numerous infections. Several studies show that most of the benzimidazole compounds can discover in nature [46], such as vitamin B12. Furthermore, these types of molecules have a noteworthy place in organic chemistry as they have natural exercises of pharmacological activity such as anticancer, antimicrobial, antidiabetic, antioxidant, and antitubercular [47]. Synthesizing an expansive number of benzimidazole moiety over a wide extend of therapeutic properties with preferential geometries [48] seems the importance of the compound within the medical industry. Particularly, benzimidazole and nitroimidazole derivatives show solid inhibition activity against breast cancer-associated proteins, such as epidermal growth factor receptor [49] (EGFR) and estrogen receptor [50] (ERα) which are mostly used as a targeted protein for breast cancer drug designing. In the literature survey, the DFT-B3LYP computational studies on 5-nitrobenzimidazole (5NBZ) have not been found. Consequently, in the current examination, the optimized parameters, vibrational frequencies and molecular orbital energies such as charge density dispersions of 5NBZ are computed.

3. OBJECTIVES

Some pure compounds having biological and pharmaceutical importance are purchased from Chemical Companies. Then these samples are subjected for taking the FTIR and FT-Raman spectral measurements. The vibrational spectroscopic characterizations have been carried out by applying IR and Raman tools, which are used for the interpretation of symmetries of molecular vibrations and to understand the identification of functional groups and various properties of the molecules. The computational details like minimum energy, moleculer geometry optimizations, thermodynamical properties, vibrational frequency calculations, IR intensity, Raman activity and the force field calculations are done by using GAUSSIAN 09W program [51] exploiting B3LYP functional [52,53] accompanied with the standard B3LYP [54] and cc-pVTZ [55] basis sets. Initially, the structure of molecules were optimized, and after that the vibrational wavenumbers, electronic properties such as highest occupied and lowest unoccupied molecular orbitals (HOMO-LUMO) [56], Molecular electrostatic potential (MEP) [57], Mulliken charge [58], Nuclear Magnetic Resonance [59] (^{13}C NMR, ^{1}H NMR), Ultraviolet visible (UV-vis) [60] spectroscopic studies, Natural bond orbital (NBO) [61] analysis have been calculated. The scaled quantum mechanical [62] (SQM) method ensures the enhanced assertion between the experimental and DFT computed values. The MOLVIB Program (Adaptation V7.0-

G77) by Sundius [63] is used in the calculation of the total energy distribution (TED) for distinctive vibrational modes. Molecular docking is most often employed in the field of pharmaceutical drug design, as the majority of drugs are composed of tiny organic molecules. The structure of proteins was taken from Protein Information Bank (http://www.pdb.org) [64]. The molecules have been taken as ligands, and their structures were gotten from the open ligand databases [65]: PubChem (http://pubchem.ncbi.nlm.nih.gov). Discovery Studio (Adaptation: 2017 R2 client) [66] program have been utilized to assess the protein structure and amino corrosive location by docking interaction with the molecules. The Molecular Docking (MD) is performed by Auto Dock Vina (Adaptation: 4.2.1) [67]. Utilizing the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)-SAR prediction tool [68], the toxicity of the systems have been assessed.

By knowing these properties of the molecules of biological activity, it can be used in different fields of applications.

4. RESEARCH PROBLEM

Over the past few years, a significant measure of exploration work has been performed to recognize potential drug molecules to inhibit the proteins which are responsible for various diseases. Also, a very big problem in our country is how to safeguard our life from emerging diseases. This can be solved only by injecting proper antibiotics to the human body. Most of the medical education and research institutes in our country were undergoing research in the synthesis of organic drugs. The vibrational spectroscopic studies of biologically active molecules are of great interest in biochemical, pharmaceutical, electro-optical and many other industries because of their applications. Hence, the biological properties of the selected molecules are needed for their various biological and pharmaceutical applications.

Further, the density functional theory is progressively becoming vital for the drug designing process. Since past few years DFT has appeared as a Quantum Mechanical (QM) method which is satisfactorily meticulous as well as competent to be employed in pharmaceutical studies. Biologically important molecular systems can be exactly described using DFT at a lesser computational cost than other methods making it a highly utilized technique. From the survey of literature, it is found that the DFT studies and biological properties of the selected compounds have not been studied so far. Therefore in order to understand the detailed information about the properties of these compounds, the present work has been carried out.

5. ORGANIZATION OF THESIS

The thesis comprises of **TEN** chapters.

Chapter 1

Chapter one deals with the theory of vibrational spectroscopy, a brief description of scaled quantum mechanical calculations and its recent advances. The selection rules for IR and Raman spectroscopy have also been discussed. The recording of spectra, the instrumentation of IR and Raman spectrophotometers and the sample handling techniques are the subject matter for chapter one.

Chapter 2

In chapter two, the reviews of literature for the selected biomolecules in this study are detailed.

Chapter 3

In the chapter three, the vibrational spectra of 2,3-dichloro-1,4-naphthoquinone (DCNQ) were recorded and complete vibrational assignment and analysis of the fundamental modes were carried out. Subsequently these were confirmed by TED. Calculations were performed by using the DFT/B3LYP method with 6-31+G(d,p) and 6-311++G(d,p) basis sets, and the optimum molecular geometry, harmonic vibrational frequencies, infrared intensities and Raman scattering activities were determined. The effects of frontier orbitals, NBO, Mulliken charges, NMR analysis and the transition of electron density transfer have been discussed. The molecular docking and ADMET studies confirms that the DCNQ acts as an inhibitor of acetylcholinesterase (4EY7 and 4EY8) proteins, which are important in therapeutic movement. All the above results are discussed in the chapter 3.

Chapter 4

In chapter four, the investigation has progressively centered on improving treatments, such as anti-angiogenic and anti-hepatoma drugs. In this consider, the conceivable inhibitory action of α-santonin which has a good interacting affinity with the active protein sites of human SARS-COV2 and cervical cancer. The molecular properties such as NBO, MEP, HOMO-LUMO, Mulliken charge, UV and NMR studies have been performed by the DFT-B3LYP strategy. The molecular docking and ADMET outcomes explain that the α-santonin particle can be utilized as a specialist within the worldwide fight against SARS-CoV-2, cancer treatment and are detailed in chapter 4.

Chapter 5

In chapter five, the vibrational spectra for 4-hydroxy-3-methylbenzoic acid (HMBA) were recorded and assignments of normal modes of the molecule were subsequently established by TED. The DFT calculations were performed and compared with the wavenumbers of the observed results. The HOMO-LUMO charge transfer interactions of the molecule which are the key factor for biological activity have been discussed. Further, the electronic properties of molecule have been examined by the Mulliken's charge and MEP analyses. The NBO, UV and NMR analysis of the molecule have been performed. The molecular docking and ADMET results exposed that the HMBA acts as an inhibitor of SARS-CoV-2 M^{pro} (6WNP) protein, which are sufficient in SARS-CoV-2 M^{pro} actions. These outcomes are discussed in the chapter 5.

Chapter 6

Chapter six is concerned with the molecular vibrations of 3-methoxy-2,4,5-trifluorobenzoic acid (MFBA) were studied by recording the FTIR and FT-Raman spectra and the vibrational frequencies have been compared with the DFT-B3LYP calculations. NBO analyses and the LUMO-HOMO energy gap of the molecule shows the intramolecular charge transfer interaction. The electrostatic potential, Mulliken charges, UV and NMR studies of MFBA have been performed. The molecular docking and ADMET process affirms that the MFBA acts as an inhibitor of SARS-CoV-2 M^{pro} protein, which is important for designing drugs and are discussed in chapter 6.

Chapter 7

In the seventh chapter, the vibrational spectra of 2,4-dimethoxyacetophenone (DMAP) have been recorded. The complete assignments of normal modes of DMAP were carried out from the experimental data and confirmed by TED. The DFT with 6-311++G(d,p) basis set have been used for calculating the optimized parameters, vibrational frequencies and intensities. The frontier molecular orbital analysis which is the key factor for biological activity has been discussed. In addition, the Mulliken's charge and MEP analyses of molecule have been examined in detail. The NBO, UV and NMR analysis of the molecule have been performed. The molecular docking and ADMET process affirms that the DMAP acts as an inhibitor of beta-glucosidase (2O9R) protein, which is important in beta-glucosidase enzymes for designing drugs. All the above are detailed in chapter 7.

Chapter 8

In the chapter 8, the theoretical and experimental vibrational spectra of 4-nitroimidazole (NIM) were studied extensively by spectroscopic techniques and DFT method. The contributions of the different modes to each wavenumber were confirmed using TED. The optimized parameters and thermodynamic properties of NIM have been computed. The HOMO-LUMO energy gap, NBO analysis, Mulliken's plot, MEP, NMR and UV studies of the molecule have been reported. The molecular docking and ADMET prediction affirms that the NIM acts as an inhibitor of insulin growth factor-1 (IGF-1-1JQH) protein, which are important in IGF-1 actions and the results are discussed in chapter 8.

Chapter 9

In the ninth chapter, the vibrational spectra of 5-nitrobenzimidazole (5NBZ) have been tested and the density functional hypothesis are carried out to guarantee the vibrational assignments. The molecular optimized limits and electronic properties of 5NBZ are explored by DFT/B3LYP strategy. The molecular orbital, Mulliken's plot, NBO and MEP properties of 5NBZ have been studied. The theoretical UV-vis and NMR spectral analysis have been performed. The molecular docking process affirms that the 5NBZ acts as an inhibitor of EGFR (Figure 1) and ERα (Figure 2) proteins, which are important in breast cancer movement. In silico ADMET analyses has also been predicted for the molecule to evaluate its efficacy and are detailed in chapter 9.

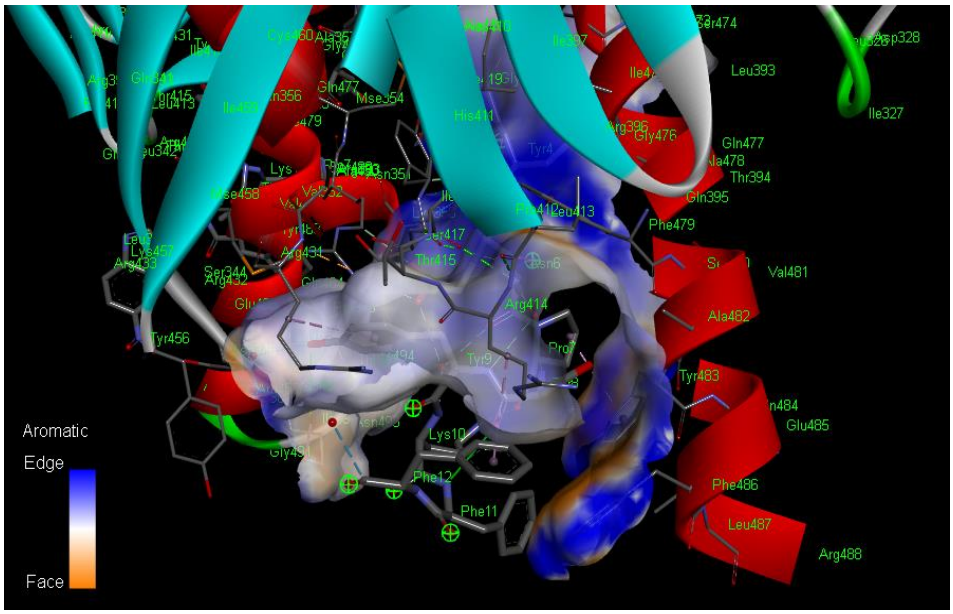

Figure 1: 5NBZ interacts with the breast cancer marker proteins includes EGFR

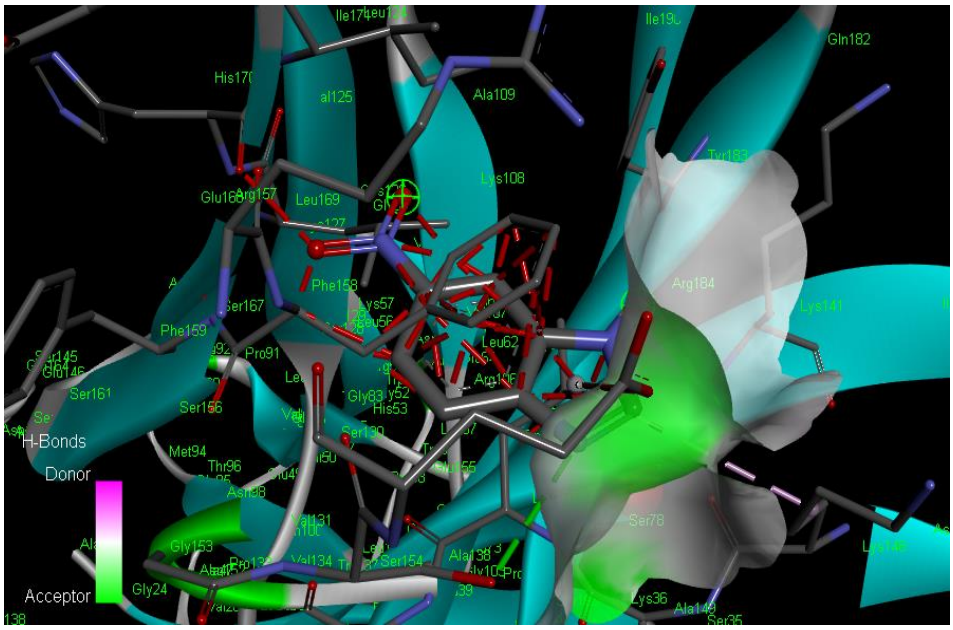

Figure 2: 5NBZ interacts with the breast cancer marker proteins includes ERα.

Chapter 10 Conclusion

The present investigation thoroughly analyzed the vibrational spectra, both infrared and Raman of some biological and pharmaceutical important compounds. The optimized parameters of molecules have been examined through DFT calculations and showed suitable agreement with the available crystal data. All the vibrational bands observed in the FTIR and FT-Raman spectra of the compounds are assigned to the various modes of vibration. The systematic comparison of results of experiments has shown that the method using scaled DFT functional is the most promising in providing correct vibrational wavenumbers. The complete vibrational assignments of wavenumbers are made on the basis of TED. The calculated HOMO and LUMO energies and NBO studies describe the $\pi \rightarrow \pi^*$, $n \rightarrow \pi$, $n \rightarrow \sigma$ interactions of the molecules, which are responsible for their bioactive property. The electronic spectra of the molecules are performed which reflects the frontier molecular orbitals. Furthermore, the thermodynamic and total dipole moment properties of the compounds have been calculated in order to get insight in to the compounds. Furthermore, Mulliken's charge and reactive sites of MEP surface clarify that the negative and positive potential spots. Docking studies explains the binding interactions of the molecules with proteins. ADMET parameters exposed that the selected molecules will be suitable candidate for medical applications with low side effects. These results will help researchers to design and synthesis new materials and also useful in biochemical, pharmaceutical, electro-optical and many other industries.

Further, they may be helpful to the scientists who were doing research on the functions of the cells in living organisms and in the drug synthesis of antimalarial, antibacterial and antifungal activity. All the outcomes are discussed in chapter 10.

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